

Claims**1. Glycinamide derivatives of formula I**

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A-D-B

(I)

wherein

D is a bivalent glycine amide moiety, or a derivative therof,

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A is a unsubstituted or substituted moiety of up to 40 carbon atoms of the formula: $-L-(M-L')^{\alpha}$, where L is a 5, 6 or 7 membered cyclic structure, preferably selected from the group consisting of aryl, heteroaryl, arylene and heteroarylene, bound directly to D, L' comprises an optionally substituted cyclic moiety having at least 5 members, preferably selected from the group consisting of aryl, heteroaryl, aralkyl, cycloalkyl and heterocyclyl, M is a bond or a bridging group having at least one atom, α is an integer of from 1-4; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein L' is preferably substituted by at least one substituent selected from the group consisting of $-SO_3R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

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B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms, preferably of up to 20 carbon atoms, comprising at least one 5-, 6-, or 7-membered cyclic structure, preferably a 5- or 6-membered cyclic structure, bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein said cyclic structure directly bound to D is preferably selected from the group

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consisting of aryl, heteroaryl and heterocyclil, R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

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R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

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R_x is R_z or NR_aR_b, where R_a and R_b are

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a) independently hydrogen, a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

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-OSi(R_f)₃ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

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or

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- 5 b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or
- 10 c) one of R_a or R_b is -C(O)-, a C₁-C₅ divalent alkylene group or a substituted C₁-C₅ divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C₁-C₅ divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;
- 15 where B is substituted, L is substituted or L' is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_γ; where γ is 0-3;
- 20 wherein each W is independently selected from the group consisting of -CN, -CO₂R, -C(O)NR⁵R⁵, -C(O)-R⁵, -NO₂, -OR⁵, -SR⁵, -SO₂R⁵, -SO₃H, -NR⁵R⁵, -NR⁵C(O)OR⁵, -NR⁵C(O)R⁵, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the groups
- 25 consisting of -CN, -CO₂R, -C(O)NR⁵R⁵, -C(O)-R⁵, -NO₂, -OR⁵, -SR⁵, -SO₂R⁵, -SO₃H, -NR⁵R⁵, -NR⁵C(O)OR⁵, -
- 30 OR⁵, -SR⁵, -SO₂R⁵, -SO₃H, -NR⁵R⁵, -NR⁵C(O)OR⁵, -

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- NR⁵C(O)R⁵ and halogen up to per-halo; with each R⁵ independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, wherein Q is -O-, -S-, -N(R⁵)-, -(CH₂)_β, -C(O)-, -CH(OH)-, -(CH₂)_βO-, -(CH₂)_βS-, -(CH₂)_βN(R⁵)-, -O(CH₂)_β, -CHHal-, -CHAl₂-, -S-(CH₂)- and -N(R⁵)(CH₂)_β- where β = 1-3, and Hal is halogen; and Ar is 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{δ1} wherein δ1 is 0 to 3 and each Z is independently selected from the group consisting -CN, -CO₂R⁵, -C(O)NR⁵R⁵, -C(O)-R⁵, -NO₂, -OR⁵, -SR⁵, -SO₂R⁵, -SO₃H, -NR⁵R⁵, -NR⁵C(O)OR⁵, -NR⁵C(O)R⁵, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO₂R⁵, -C(O)NR⁵R⁵, -C(O)-R⁵, -NO₂, -OR⁵, -SR⁵, -SO₂R⁵, -SO₃H, -NR⁵R⁵, -NR⁵C(O)OR⁵, -NR⁵C(O)R⁵, and the physiologically acceptable derivatives, salts and solvates thereof.
- 25 2. Glycinamide derivative according to claim 1, characterised in that each M independently from one another represents a bond or is a bridging group, selected from the group consisting of (CR⁵R⁵)_h, or (CHR⁵)_h-Q-(CHR⁵)_l, wherein
- 30 Q is selected from a group consisting of O, S, N-R⁵, (CHAl₂)_j, (O-CHR⁵)_j, (CHR⁵-O)_j, CR⁵=CR⁵, (O-CHR⁵CHR⁵)_j,

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($\text{CHR}^5\text{CHR}^5\text{-O}$)_j, C=O, C=S, C=NR⁵, CH(OR⁵), C(OR⁵)(OR⁵), C(=O)O, OC(=O), OC(=O)O, (C=O)N(R⁵)C(=O), OC(=O)N(R⁵), N(R⁵)C(=O)O, CH=N-NR⁵, S=O, SO₂, SO₂NR⁵ und NR⁵SO₂,
wherein

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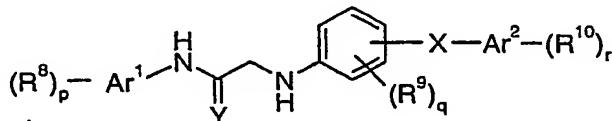
R⁵ is in each case independently selected from the meanings given above, preferably hydrogen, halogen, alkyl, aryl, aralkyl,

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h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6,
preferably 0, 1, 2 or 3, and

i is 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3.

15 3. Glycinamide derivative according to claim 1 or 2, selected from the
compounds of formula II,



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20 wherein

Ar¹, Ar² are selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two hetero atoms, independently selected from N, O und S,

R⁸, R⁹

30 and R¹⁰ are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, C(Hal)₃, NO₂, (CH₂)_nCN,

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- (CH₂)_nNR¹¹R¹², (CH₂)_nOR¹¹, (CH₂)_nO(CH₂)_kNR¹¹R¹²,
 (CH₂)_nCOOR¹², (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³,
 (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A,
 (CH₂)_nSO₂NR¹¹R¹², (CH₂)_nS(O)_uR¹³, (CH₂)_nOC(O)R¹³,
 5 (CH₂)_nCOR¹³, (CH₂)_nSR¹¹, CH=N-OA, CH₂CH=N-OA,
 (CH₂)_nNHOA, (CH₂)_nCH=N-R¹¹, (CH₂)_nOC(O)NR¹¹R¹²,
 (CH₂)_nNR¹¹COOR¹², (CH₂)_nN(R¹¹)CH₂CH₂OR¹³,
 (CH₂)_nN(R¹¹)CH₂CH₂OCF₃, (CH₂)_nN(R¹¹)C(R¹³)HCOOR¹²,
 C(R¹³)HCOR¹², (CH₂)_nN(R¹¹)CH₂CH₂N(R¹²)CH₂COOR¹²,
 10 (CH₂)_nN(R¹¹)CH₂CH₂NR¹¹R¹², CH=CHCOOR¹¹,
 CH=CHCH₂NR¹¹R¹², CH=CHCH₂NR¹¹R¹²,
 CH=CHCH₂OR¹³, (CH₂)_nN(COOR¹¹)COOR¹²,
 (CH₂)_nN(CONH₂)COOR¹¹, (CH₂)_nN(CONH₂)CONH₂,
 (CH₂)_nN(CH₂COOR¹¹)COOR¹²,
 15 (CH₂)_nN(CH₂CONH₂)COOR¹¹,
 (CH₂)_nN(CH₂CONH₂)CONH₂, (CH₂)_nCHR¹³COR¹¹,
 (CH₂)_nCHR¹³COOR¹¹, (CH₂)_nCHR¹³CH₂OR¹⁴, (CH₂)_nOCN
 and (CH₂)_nNCO, wherein
- 20 R¹¹, R¹² are independently selected from a group consisting of H, A, (CH₂)_mAr³ and (CH₂)_mHet, or in NR¹¹R¹²,
- 25 R¹¹ and R¹² form, together with the N-Atom they are bound to, a 5-, 6- or 7-membered heterocyclo which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S,
- 30 R¹³, R¹⁴ are independently selected from a group consisting of H, Hal, A, (CH₂)_mAr⁴ and (CH₂)_mHet,
- A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylene cycloalkyl, alkoxy and alkoxyalkyl,

- 5 Ar^3, Ar^4 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{R}^{15}\text{R}^{16}$, $\text{S(O)}_u\text{A}$ and OOCR^{15} ,
- 10 Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , 15 $\text{SO}_2\text{R}^{15}\text{R}^{16}$, $\text{S(O)}_u\text{A}$ and OOCR^{15} ,
- 20 $\text{R}^{15}, \text{R}^{16}$ are independently selected from a group consisting of H, A, and $(\text{CH}_2)_m\text{Ar}^5$, wherein
- 25 Ar^6 is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3 ,
- 30 n, m are independently of one another 0, 1, 2, 3, 4, or 5;
- X represents a bond or is $(\text{CR}^{11}\text{R}^{12})_h$, or $(\text{CHR}^{11})_h\text{-Q-}(\text{CHR}^{12})_i$, wherein
- Q is selected from a group consisting of O, S, N-R¹⁵, $(\text{CHal}_2)_j$, $(\text{O-CHR}^{18})_j$, $(\text{CHR}^{18}-\text{O})_j$, $\text{CR}^{18}=\text{CR}^{19}$, $(\text{O-CHR}^{18}\text{CHR}^{19})_j$, $\text{CHR}^{18}\text{CHR}^{19}-\text{O}_j$, C=O, C=S, C=NR¹⁵, CH(OR^{15}),

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C(OR¹⁷)(OR²⁰), C(=O)O, OC(=O), OC(=O)O, C(=)N(R¹⁵),
N(R¹⁵)C(=O), OC(=O)N(R¹⁵), N(R¹⁵)C(=O)O, CH=N-O,
CH=N-NR¹⁵, OC(O)NR¹⁵, NR¹⁵C(O)O, S=O, SO₂, SO₂NR¹⁵
und NR¹⁵SO₂, wherein

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h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6, and

j is 1, 2, 3, 4, 5 or 6,

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Y is selected from O, S, NR²¹, C(R²²)-NO₂, C(R²²)-CN and
C(CN)₂, wherein

R²¹ is independently selected from the meanings given for R¹³,
R¹⁴, and

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R²² is independently selected from the meanings given for R¹¹,
R¹²,

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p, r are independently from one another 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

u is 0, 1, 2 or 3, preferably 0, 1 or 2,

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and

Hal is independently selected from a group consisting of F, Cl,
Br and I;

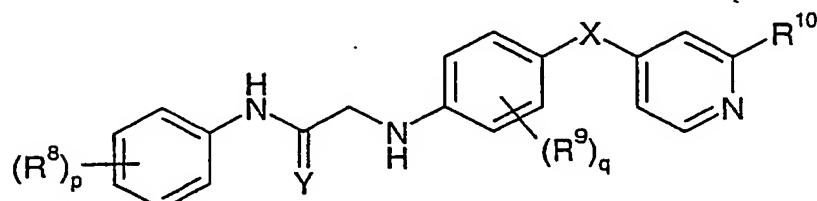
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and the salts and solvates thereof.

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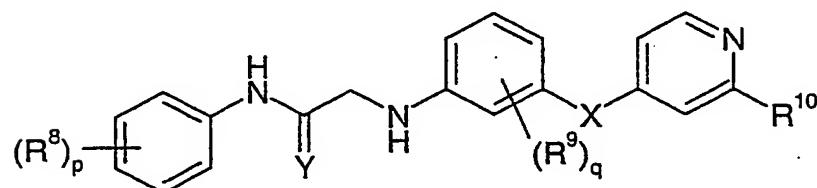
4. Glycinamide derivative according to one of the claims 1 to 3, selected from the compounds of formula IIa, IIb, IIc, IId, IIe, IIf, IIg and IIh,

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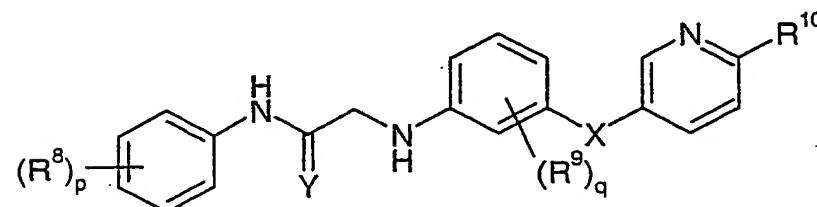
IIa

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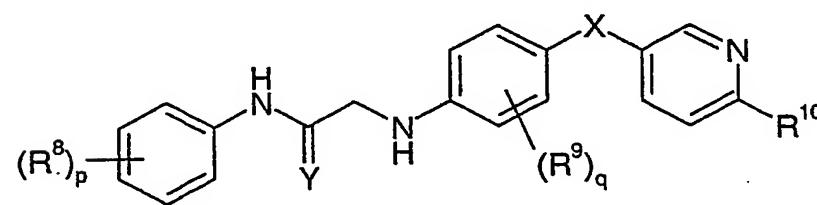
IIb

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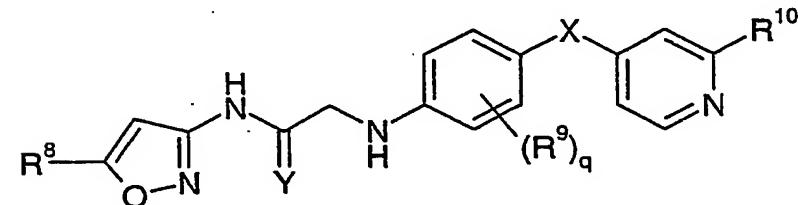
IIc

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IId

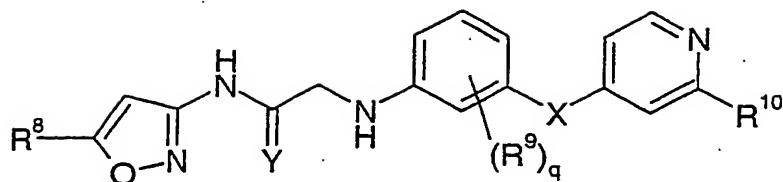
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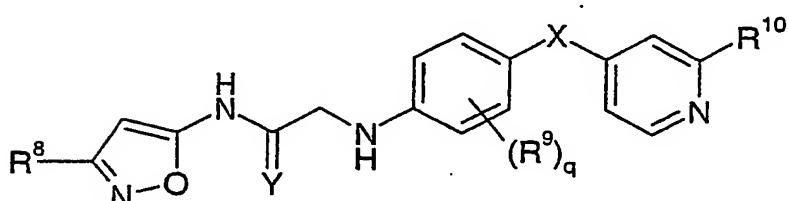
IIe

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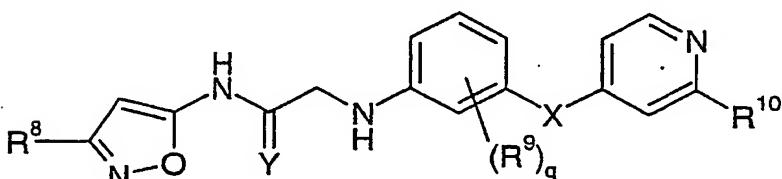
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III f



II g

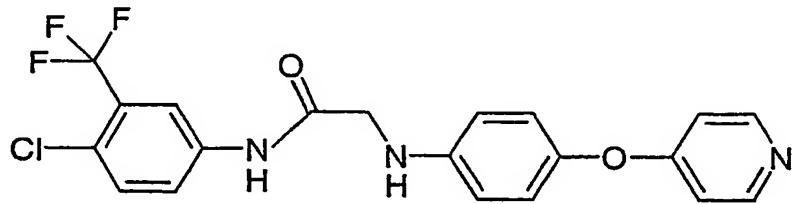


II h

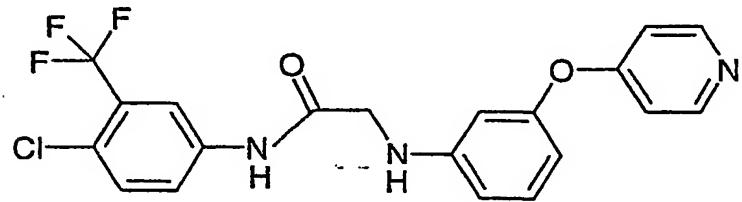
wherein R⁸, p, Y, R⁹ and q are as defined in claim 3, and R¹⁰ is H or as defined in claim 3; and the salts and solvates thereof.

5. Glycinamide derivative according to claim 1 or 2, selected from

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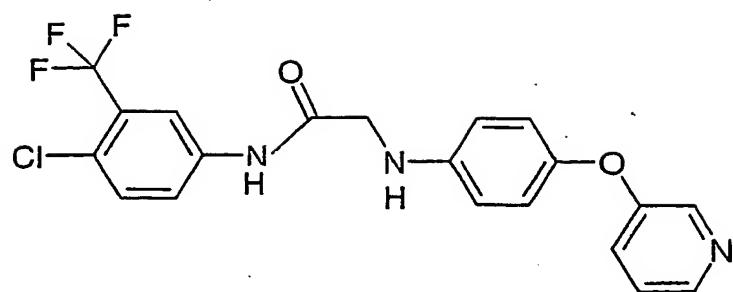


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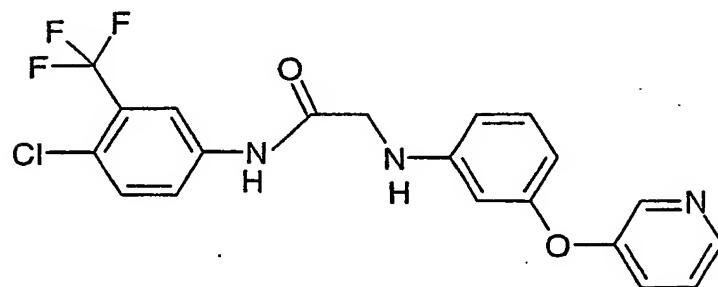


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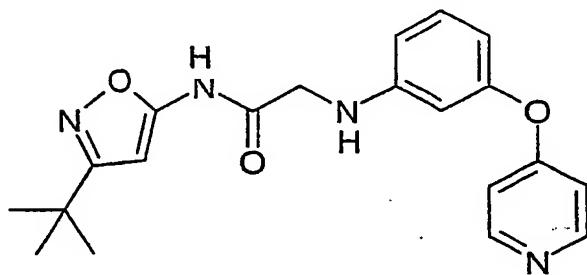


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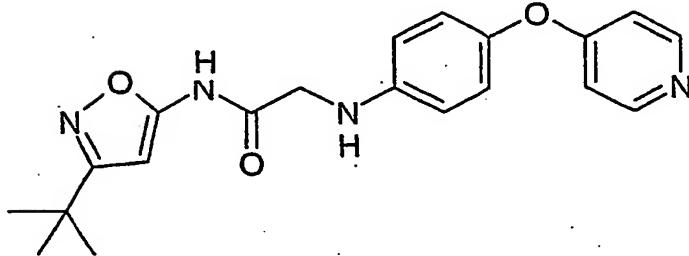
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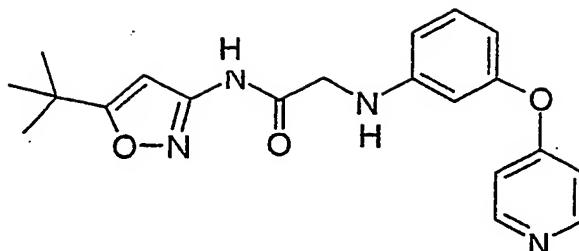
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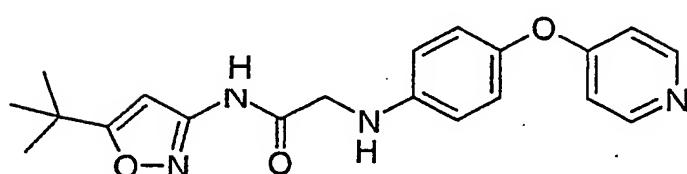


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6. Glycinamide derivative according to one of the claims 1 to 5 as a medicament.

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7. Glycinamide derivative according to one of the claims 1 to 5 as a kinase inhibitor.

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8. Glycinamide derivative according to claim 7, characterized in that the kinases are selected from raf-kinases.

9. Pharmaceutical composition, characterized in that it contains one or more compounds according to one of the claims 1 to 5.

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10. Pharmaceutical composition according to claim 9, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5.

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11. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the

- claims 1 to 5 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5, is processed by mechanical means into a
- 5 pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.
12. Use of a compound according to one of the claims 1 to 5 as a pharmaceutical.
- 10 13. Use of a compound according to one of the claims 1 to 5 in the treatment and/or prophylaxis of disorders.
14. Use of a compound according to one of the claims 1 to 5 for
- 15 producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.
15. Use according to claim 13 or 14, characterised in that the disorders are caused, mediated and/or propagated by raf-kinases.
- 20 16. Use according to claim 13, 14 or 15, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.
- 25 17. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is cancer.
18. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is noncancerous.
- 30 19. Use according to claim 13, 14, 15, 16 or 18, characterised in that the noncancerous disorders are selected from the group consisting of

infection, psoriasis, arthritis, inflammation, endometriosis, scarring, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.

- 5 20. Use according to one of the claims 13 to 17, characterised in that the disorders are selected from the group consisting of brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, 10 gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.
- 15 21. Use according to one of the claims 13 to 16, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation and neurodegenerative diseases.
- 20 22. Use of a compound according to one of the claims 1 to 5 as a raf-kinase inhibitor.
- 25 23. Use according to claim 22, characterised in that the raf-kinase is selected from the group consisting of A-Raf, B-Raf and c-Raf-1.
- 30 24. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 5 is administered to a patient in need of such a treatment.
25. Method according to claim 24, characterised in that the one or more compounds according to one of the claims claim 1 to 5 are

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administered as a pharmaceutical composition according to claim 9 or 10.

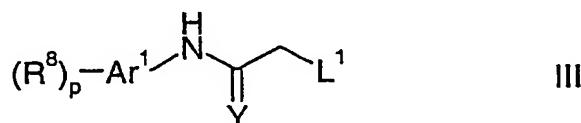
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26. Method for the treatment and/or prophylaxis of disorders according to
claim 25, characterised in that the disorders are as defined in one of
the claims 15 to 21.

27. Method for the treatment according to claim 26, characterised in that
the disorders is cancerous cell growth mediated by raf-kinase.

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28. Method for producing compounds of formula II, characterised in that

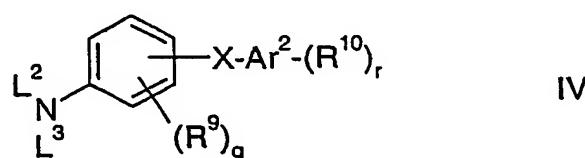


wherein

L^1 is Cl, Br, I, OH, a reactive esterified OH-group or a diazonium moiety, and R^8 , p, Ar^1 , Y are as defined in claim 3,

is reacted

b) with a compound of formula IV.



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wherein

L^2 , L^3 are independently from one another H or a metal ion, and R^9 ,
 q , X , Ar^2 , R^{10} and r are as defined in claim 3,

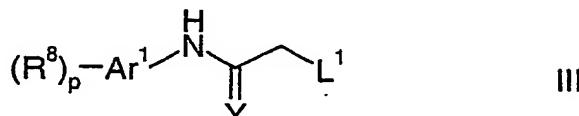
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and optionally

isolating and/or treating the compound of formula II obtained by said reaction with an acid, to obtain the salt thereof.

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29. Compound of formula III,



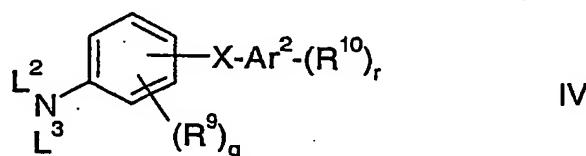
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wherein

L^1 is Cl, Br, I, OH, a reactive esterified OH-group or a diazonium moiety, and R^8 , p , Ar^1 , Y are as defined in claim 3.

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30. Compound of formula IV,



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wherein

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L^2 , L^3 are independently from one another H or a metal ion, and R^9 , q , X , Ar^2 , R^{10} and r are as defined in claim 3.